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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,653	QASBA ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 6-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is a continuation of 09/316,797, filed May 21, 1999, which claims benefit to 60/086,420, filed May 22, 1998 and 60/108,308, filed November 13, 1998.

Applicants' amendment filed October 9, 2003, has been received and entered. Claims 4 and 5 have been amended. Claims 1-8 are pending.

Election/Restriction

Applicant's election of group II, claims 4 and 5, in Paper No. 3, was acknowledged. It was noted that because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-8 are pending. Claims 1-3, 6-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 4 and 5 are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

This application contains claims drawn to nonelected invention elected with traverse (see paper 3, page 1). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

This application lacks the necessary reference to the prior application. A statement reading "This is a continuation of Application No. 09/316,797, filed May 21, 1999." should be entered following the title of the invention or as the first sentence of the specification. Also, the current status of all nonprovisional parent applications referenced should be included.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 5 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a subject in need of megakaryocytes as platelet precursor cells comprising administering to said subject autologous or allogenic bone marrow in an amount effective to produce megakaryocytes, does not reasonably provide enablement for

administering only mesenchymal stem cells or mesenchymal stem cells and CD34+ cells alone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants note that the burden of proof to show that a particular method is not effective is upon Examiner not Applicants (see top of page 4). Applicants summarize the basis of the rejection and argue that the Examiner has not provided evidence that the method when practiced *in vivo* would not work . Additionally, Applicants note the claims require treating a patient in need of megakaryocytes, which includes alleviation of a disease or condition, as well as a cure , and does not exclude practice of the claimed method in conjunction with other forms of treatments (middle of page 4). Applicants argue that it would be contrary to the interests of justice to limit the scope of protection to specific patients and that infringement of the broad scope of Applicants' inventive discovery could be avoided by treating patients outside the scope of the claims (bottom of page 4). Finally, Applicants argue that the claimed methods require administering mesenchymal stem cells and not mesenchymal cells *per se*, and that the Examiner has not provided any evidence that administration of mesenchymal stem cells would not be sufficient to restore megakaryocytopoiesis (page 5). Further, it is noted that the evidence provided by the Examiner has demonstrated that mesenchymal cells are capable of supporting the differentiation of $CD34^+$ hematopoietic stem cells into megakaryocytes and thus it would not be an undue burden to administer both these cells *in vivo* to produce megakaryocytes with a

reasonable expectation of success (page 6). See Applicants' amendment, starting on bottom of page 4 to page 6. Applicants' arguments have been fully considered, but not found persuasive.

It is noted that 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Further, the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Finally, case law teaches (*Ex parte Forman*, 230 USPQ 546,547 (BPAI 1986)) that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." As set forth in the previous office action, there is no working example nor guidance regarding the method of administration of mesenchymal cells on megakaryocytopoiesis *in vivo*. The specification does demonstrate that mesenchymal cells can affect CD34+ cells *in vitro*, however only refers generally to use of production of differentiated megakaryocytes (page 11, line 15), and does not disclose any guidance regarding administration or conditions to produce these affects *in vivo*. Thus the claimed invention is based on the speculation that observation made *in vitro* can be simply extended to method *in vivo*. In this

case, lacking any specific examples in the art or the specification demonstrating the claimed invention is fully enabled, the Examiner must access that basis of the invention and whether simple *in vitro* experiments can be extended to working methods of treatment in a more complex *in vivo* system. It is noted that Applicants' do not specifically discuss or dispute the evidence provided in the cited references of Ellis *et al.*, Berenson *et al.*, Bertolini *et al.* or Emerson used in the basis of the rejection, only that Examiner relies on speculation. This argument is not found persuasive because sound scientific arguments based on cited references is provided by the Examiner. Moreover, the Examiner has set forth in the basis of the rejection each of Wands factors. Examiner acknowledges that the burden of proof lies first with the office, however in this case a *prima facie* case demonstrating limitations recognized in the art has been established and a review of the teaching of the specification has been done demonstrating that the teachings therein fail to adequately address the art recognized problems. It is noted and acknowledged that there is no specific statement in any of the cited references that practicing the claimed method would not work. However, each of the cited references provide specific limitations recognized in the art at the time of filing that would have to be overcome in order to practice the claimed invention in the full breadth as instantly claimed for both claims 4 and 5

. As noted previously in the basis of the rejection, the specification is silent with respect to any disease or condition in which only megakaryocytes are required. Examiner would agree that claimed method if enabled could be practiced with other methods of treatment known in the art, however the specification does not provide any specific guidance to what these other treatments

are or how they would be combined with the instantly claimed methods. Again, the reasons and/or circumstances of 'a patient in need of megakaryocytes' alone are not specifically discussed or defined in the specification or the art of record, which has bearing on the predictability of treating a patient in need thereof, because the effective amount to be administered can not be clearly assessed lacking any specific condition or disease to be treated. Thus, while claim 5 encompasses administering CD34+ cells which have the potential to differentiate into megakaryocytes, the specification lacks any guidance on how the cells would be administered, at what concentration for what diseases of conditions. Again there is no working example nor guidance regarding the method of administration of mesenchymal cells on megakaryocytopoiesis *in vivo*. The specification demonstrates that mesenchymal cells can affect CD34+ cells *in vitro*, and only refers generally to use of production of differentiated megakaryocytes (page 11, line 15), and does not disclose any guidance regarding administration or conditions to produce these affects *in vivo*.

The claimed methods comprises administering mesenchymal stem cells and relies on the ability to promote megakaryocyte differentiation of CD34+ cells as observed in *in vitro* studies. It was known in the art that the CD34+ hematopoietic stem cells are the cells in the bone marrow capable of differentiating and giving rise to multiple lineages including megakaryocytes. Thus, even if one were to treat individuals receiving chemotherapy, a bone marrow transplant or a peripheral blood stem cell transplants none of these subjects contain the CD34+ hematopoietic stem cells which are necessary and capable of being induced and differentiating into

megakaryocytes. Thus, claim 4 encompasses providing mesenchymal stem cells to a subject under conditions wherein the cells required, the CD34+ cells, are not present.

With respect to the delivery of any type mesenchymal stem cell, Examiner acknowledges that the claims do not encompass simply providing a mesenchymal cell. However, the specification clearly contemplates sources other than the bone marrow, though the preferred source is the bone marrow (page 6; line 12). To this end, the claims encompass the use of mesenchymal stem cells from other tissue sources. The specification provides no guidance to methods for isolating mesenchymal stem cells from other tissues, nor if such cells were isolated or exist, if they would possess the properties of mesenchymal stem cells isolated from the bone marrow. Examiner has cited Dexter *et al.* to demonstrate that 'cells from the spleen, liver, or other tissues do not support hemopoiesis *in vitro*' (page 432, first column). Clearly, if these cells sources can not support growth *in vitro*, there is little expectation that they would obtain new properties and support any growth *in vivo*. The physiological art in general is acknowledged to be unpredictable (MPEP 2146.03). To this end Examiner has cited Emerson who reviews the success of expanded bone marrow cultures ability to recover megakaryocytopoiesis in patients (page 3085; section on INITIAL CLINICAL EXPERIENCE...), and described the successful engraftment of *ex vivo* expanded CD34+ cells (last paragraph). However, all the methods described to restore megakaryocytopoiesis *in vivo* have relied on administration of a "stem cell" or "progenitor cell" which is capable of differentiating into the desired cell type, and to date, there is no report that administration of a "mesenchymal cell"

would produce the same effect as a "stem cell" upon administration. The specification does not demonstrate nor disclose prior art demonstrating that differentiation effects of isolated mesenchymal cells can occur *in vivo* when administered to a patient. With respect to claim 4 applicant makes the supposition that a stem cell capable of producing a megakaryocyte is present *in vivo*, and with respect to claim 5, that administration of both mesenchymal supporting and stem cell would allow for megakaryocytopoiesis.

In addition, beyond the general teaching of the specification for deficiencies of megakaryocytes in a subject, the art teaches that the presence of low amounts of megakaryocytes can be due to physiological conditions as is found in thrombocytopenia, megaloblastic anemia, or in a patient who is deficient in folate or Cbl where maturation of megakaryocytes can be disrupted (Handin *et al.*, pages 1399-1401). In these instances, the lack of megakaryocytes is due to an inhibition of differentiation of CD34+ hematopoietic stem cells. Therefore, a method of treatment as stated in claims 4 or 5 would not produce megakaryocytes in such a patient in need of megakaryocytes because the claimed method does not remedy nor address the fundamental physiological problem in these types of subjects.

Finally, the claims are not limited to administering autologous or allogenic mesenchymal stem cells, and broadly encompass xenogeneic cell transplantation which to date has not been successfully performed for any form of treatment. The specification specifically contemplates using non-matched donor cells (page 6, lines 4-6), and therefore encompasses transplantation of cells to a subject from an unrelated species. In both cases the specification is silent with respect

to any discussion or guidance to overcome these long time art recognized limitations. It is noted that Applicants have not addressed this specific issue in the traversal and have not amended the claims accordingly.

35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), and that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Furthermore, the courts have held that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In the instant case there is no disclosure of even one working example *in vivo*. As discussed above, subjects contemplated by the specification as needing megakaryocytes are patients in which most or all of the hematopoietic system has been impaired or destroyed. Therefore, these patients lack hematopoietic stem cells which are capable of differentiating into megakaryocytes. In these patients administering mesenchymal stem cells will have no affect on megakaryocyte formation because the required cell types mesenchymal stem cells could potentially affect are not even present. The specification is silent to discussion of any other conditions requiring megakaryocytes, and in view of the art, the physiologically basis of these disorders would indicate that the claimed methods would not remedy their fundamental deficiencies.

Enablement has been considered in view of the Wands factors (MPEP 2164.01(a)). The factors considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

The prior art demonstrates that megakaryocyte development is a complex, multi-step process dependent on numerous positive and negative affecters as well as specific cell-cell interaction (page 1, summary of thromboiesis by Ellis *et al.*) It is noted that differentiation of progenitor cells into megakaryocytes *in vitro* has be achieved using various culturing conditions and addition of growth/stimulating factors to the media, and that explant of bone marrow, in particular the CD34+ hematopoietic stem cells in the marrow are capable of differentiating into megakaryocytes *in vivo*. Applicants have defined a potential use of an *in vivo* method of treatment using mesenchymal cells, but essentially have left all of the work required to develop a working method *in vivo* for any patient in need of megakaryocytes has been left to others. The specification fails to provide the necessary guidance to overcome art recognized limitations encompassed by the breadth of the claims and fails to provide a nexus from observations made in an *in vitro* culture system to an *in vivo* method of treatment of a patient.

Therefore, for the reasons above and of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4 and 5 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lemoli *et al.* (Acta Haematologica 95:164-170, (1996)) as evidenced in Developmental Biology (page 357).

Applicants summarize the invention and the teaching of Lemoli *et al.* and argue that Lemoli *et al.* does not disclose the isolation of mesnechymal stem cells or the administration of isolated mesenchymal stem cells to a patient. See Applicants' amendment top of page 3. Applicants' arguments have been fully considered but not found persuasive.

It is noted that the claims have been amended to recite administration of isolated human mesenchymal stem cells, however the term "isolated" is a broad general term encompassing the removal of sample from a location it is normally found. Applicants arguments that the claimed invention is differentiated from that disclosed in the art appears to focus on the use of a 'purified' preparation of mesenchymal stem cells. In the instant case the removal of bone marrow from an

individual containing mesenchymal stem cells would be considered 'isolated' from the subject. Applicants arguments are not found persuasive because Lemoli *et al.* teach the administration of isolated samples, in particular the adminstration of bone marrow isolated from a subject. Applicants do not contest the fact that mesenchymal stem cells are found in bone marrow, therefore the isolated bone marrow samples containing mesenchymal stem cells anticipates the claims as instantly amended. As noted in the basis of the previous rejection, with respect to the single method step recited in the claims, the administration of mesenchymal stem cells (claim 4) and the administration of mesenchymal stem cells and CD34+ cells is broad encompassing any means of delivery and the delivery of the cells in any composition. The specification contemplates **any** process of obtaining mesenchymal stem cells or co-recovery of hematopoietic progenitor cells and mesenchymal stem cells (page 6, lines 18-24) which could subsequently be used in the claimed methods. The specification teaches that a preferred source of mesenchymal stem cells is the bone marrow (page 6, lines 11-12). Accordingly, a reasonable interpretation of the instant claims in light of the guidance of the instant specification is a method comprising administering bone marrow to a subject who has undergone radiation therapy wherein said therapy ablates the cells of the hematopoietic system. Again, the claims are directed to providing megakaryocytes to a patient in need thereof, and while the specification is silent with respect to any specific condition wherein only megakaryocytes are required, it teaches generally that a subject in need of platelets, such as individuals receiving chemotherapy or bone marrow transplant, would benefit from the instantly claimed method (page 8, lines 8-12).

As set forth in the basis of the previous rejection, Lemoli *et al.* teach a method of autologous bone marrow transplantation to patients undergoing myeloablative chemotherapy (page 165, Study Design section). Specifically, bone marrow was removed from the patient before chemotherapeutic treatment (page 165, BM samples section). Analysis of the patients after myeloablative treatment and delivery of the autologous bone marrow indicated that an increase in platelets could be detected (summarized in figure 2, lower graph). Lemoli *et al.* does not specifically characterize or state that megakaryocytes are produced by this procedure, however the formation of platelets, the end product of megakaryocyte differentiation, is a clear indication that megakaryocytes are formed in the subject (see figure 9.39 on page 357 in Developmental Biology as evidence of megakaryocyte differentiation pathway). Thus, the development of platelets indicates that sufficient amounts cells were administered to affect the patient. In this case, in light of the teaching and guidance of the specification the limitations of an autologous bone marrow transplant to patients who have undergone chemotherapeutic treatment, and the evidence of recovery of platelet formation in said patients after the administration of bone marrow anticipates the instantly claimed methods. As noted in the previous office action, the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to

establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

Therefore, for the reasons above and of record, the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732. After January 12, 2004, the Examiner's telephone number will be (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. After January 12, 2004, Deborah Reynolds telephone number will be (571)272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141. After January 14, 2004, Dianiece Jacobs telephone number will be (571)272-0532.

Joseph T. Woitach